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Levels of analysis in etiological research on schizophrenia

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Abstract
Etiological research spanning domains of inquiry as diverse as social psychology and molecular genetics has identified a number of potential factors that likely contribute to the development and clinical manifestation of schizophrenia. In this article, we first highlight the challenges inherent in developing cogent etiological models that represent both the diversity of suspected causal influences and their mechanisms of action. Then, using our own research program as a heuristic context, we present a general analytical framework for identifying and integrating multiple types of etiologic factors across different levels of analysis in the prediction of schizophrenia. In recognition of the myriad complexities of multifactorial causation, we argue that a multilevel causal perspective is required for the development and advancement of a fully nuanced theory of schizophrenia etiology and pathophysiology.

In schizophrenia, as in other domains of psychopathology, research has revealed a diversity of factors thought to represent causative influences (e.g., Cannon, 1997; Carlsson, 1995; Cohen & Servan–Schreiber, 1992; Karayiorgou & Gogos, 1997; Selemon & Goldman–Rakic, 1999). In some cases these factors derive from the same general domain of inquiry (e.g., anatomical brain lesion and altered neurotransmitter function), and in some cases they derive from quite disparate domains (e.g., social cognitive and biological influences). In either case, such findings imply multifactorial causation in which the various causal influences ultimately coalesce in producing a behavioral outcome but do not necessarily operate via precisely the same mechanisms. The challenge for psychopathology researchers is thus to specify etiologic models that integrate putative causal influences across multiple levels of analysis (Carpenter, 1987; Engel, 1977). The primary goal of this article is to describe an analytical framework for such integration. In so doing, we provide a conceptual overview of work conducted in our laboratory and elsewhere as it relates to a multilevel perspective on the etiology of schizophrenia.

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Typology of Causal Influences

It is important to recognize at the outset that most forms of psychopathology are complexly determined phenomena, whereby multiple causal influences that may be separated in time and place and distinct in terms of mechanism of effect, integrate in the determination of a (not necessarily static) behavioral endpoint (Cicchetti & Tucker, 1994). In considering the ways in which two or more causal influences may be integrated, it will be heuristic first to

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review concepts and terminology with regard to causal influences per se.

A critical dimension along which causal influences vary is *spatiotemporal proximity* to the behavioral endpoint in question. In psychopathology research we are typically interested in both distal and proximal causal influences, because understanding both will be critical for developing a complete model of etiology and both may present targets for therapeutic or preventive intervention (Cicchetti & Cannon, 1999). The distinction between distal and proximal causes is closely related to that between the terms *etiology* and *pathophysiology* in the field of medicine (Andreasen, 1987). Whereas distal causes typically refer to types of influences (e.g., genes, toxic exposures, etc.) that represent fundamental initiating processes relevant to disease etiology, proximal causes typically refer to the mechanisms through which distal causes achieve their effect on the behavioral endpoint (e.g., neuronal loss). As we shall see in the examples to follow, developing a framework for understanding the relationship between distal and proximal causes of psychopathology will typically involve adopting a multilevel perspective on disease causation, as the distal and proximal causes will generally differ in their mechanism(s) of causal effect in relation to the behavioral endpoint; that is, they will more often than not derive from different levels of analysis.

Another dimension along which causal influences vary is in terms of their degree or frequency of causal relation to the behavioral endpoint. In genetics this concept is expressed in the term *penetrance* (Bodmer & Cavalli–Sforza, 1976). Some causal influences are always present in the histories of patients with a particular form of psychopathology and may, on that basis, be considered *necessary* causes. Some causal influences are present *only* among patients with a particular illness (though not necessarily in every case) and are, on that basis, considered *sufficient* causes (cf., Cicchetti & Aber, 1986). A causal influence that is present in all cases of an illness, and only among individuals with that illness, is both *necessary* and *sufficient*. Finally, some causal influences are neither necessary nor sufficient but nevertheless participate causally when present; such influences are said to be *contributing* causes. In psychopathology, most distal causes are likely to be contributing influences; these may derive from quite disparate domains of inquiry or levels of analysis (e.g., stressful life events, cognitive schema, inherited predispositions). In some cases, a number of distal factors will be causally related to a behavioral endpoint via a final common pathway or mechanism. In the above parlance, such a mechanism would be considered a *proximal sufficient cause*.

It must be kept in mind that we are rarely in a position to measure putative causal influences directly. Rather, we measure indicator variables or markers of factors or processes that are suspected to be causal. In a multilevel framework, we could be investigating multiple indicators of the same fundamental causal process but from different perspectives, or we may be investigating multiple different causal processes that interact in complex ways. We will generally be in a position to know whether a particular indicator or marker variable is, strictly speaking, causal, and if so, its manner of causal relation to the behavioral endpoint, only after extensive investigation in which other interpretations of its role (e.g., as epiphenomenon) have been ruled out. An indicator variable that is in itself not causal may nevertheless be quite valuable in etiologic research; for example, such a variable may be more directly or reliably assessed than the causal factor or process that it marks.

Multilevel Causation

Multilevel causation is implied whenever two or more causal influences exert their effects on a behavioral endpoint via different mechanisms. There are at least four ways in which this causal integration may be achieved: summation, transduction, interaction, and cascade. These concepts are, of course, already familiar in etiologic research on psychopathology; the descriptions given subsequently emphasize their meanings and utility in regard to the integration of causal influences across levels of analysis. It is important to keep in mind that more than one of these forms of multi-

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level integration may apply with respect to a given behavioral endpoint, as will become clear in a later section, in which we consider a multilevel perspective on the causes of schizophrenia.

Summation

Two or more causal influences may affect the behavioral endpoint independently via different proximal mechanisms (e.g., Maziade, 1988). In this circumstance, their causal effects in relation to that endpoint are additive (i.e., their joint occurrence does not have a larger causal impact than the sum of their independent influences). This mode of integration may be relatively common in psychopathology, in which behavioral endpoints are often defined in terms of groupings of multiple symptoms and signs, the causes of which may differ. To the extent that the different symptoms or dimensions of an illness phenotype are determined independently, by different causal factors, the influences of these factors are integrated additively with respect to determination of the overall phenotype. This form of causal integration *may* apply, for example, in explaining positive and negative symptoms of schizophrenia, cognitive and vegetative symptoms of depression, and so forth.

Transduction

Some (typically distal) causal influences are transduced into proximal mechanisms of behavioral effect. Genetic influences on behavior are examples of this form. A behavioral endpoint that is under partial genetic control is not encoded directly by the genes that contribute to the trait variance. Rather, such genes encode specific proteins that operate via particular biochemical pathways. In the case of psychopathology, the relevant genes most likely affect pathways related to central nervous system (CNS) structure, physiology, and/or function. The genetic contribution to the behavioral endpoint in question is thus transduced via its effects on the CNS. It is important to emphasize that the evidence of such transduction does not necessarily mean that a complete etiologic model has been achieved. In this example, the particular CNS changes encoded by the "disease genes" are at least proximal sufficient causes of the genetic component of the trait variance, but they may not be strictly necessary for at least some cases of the disease phenotype. Likewise, although the relevant disease genes may be sufficient for producing the CNS changes that lead to the behavioral endpoint, there may be many other, nongenetic causes of such changes among the population of affected cases. It is also important to note that no form of psychopathology is under complete genetic determination, so a model specifying exclusively the genetic component of a disease phenotype is, in this context, necessarily incomplete.

Interaction

The causal influences of two or more factors on the behavioral endpoint may depend on their mutual occurrence. This form of causal integration would seem necessarily to apply to many forms of psychopathology in which a particular environmental event or condition is implicated but not all individuals exposed to that event or condition develop the illness. Some form of prior vulnerability or predisposition would seem to be required to explain this selectivity of effect. In some cases, the requisite vulnerability may have been acquired via prior environmental risk exposures. Such an interaction is suspected to play a role in the etiology of major depression, in which stressful events (e.g., the death of loved one) sensitize the brain's stress responsivity systems, resulting in a lower threshold for the subsequent activation of these systems (Heim & Nemeroff, 2001). Although both the initiating event and the subsequent stressors derive from the same domain of inquiry (i.e., social cognitive influences), their effects on the illness phenotype may depend on their proximal interactions with neurohormonal mechanisms, and vice versa. In other cases, the predisposing factors with which environmental risk exposures interact may be inherited. In this case, the "character" encoded for by the gene products is not the disease phenotype per se but a trait or traits that confer vulnerability to par-

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ticular types of environmental events or conditions.

Cascade

Influences at different levels of analysis may occur as sets of cascading influences, where a particular causal influence is transduced or otherwise integrated into another causal influence, which in turn is transduced or otherwise integrated into a third influence, and so on (cf., Cicchetti & Tucker, 1994). In this case, an influence occurring early in the cascade may or may not itself continue to be an active, operative cause of the behavioral endpoint. Certain of such influences may become "fixed," traitlike features that are *necessary* for disease vulnerability but do not participate directly in symptom formation. Integration of causal influences via cascades is intrinsic to the concept of development. Cascades are also common in neuroscience models as the effect of a particular initiating event (e.g., cell depolarization) sets off a chain reaction involving electrical, chemical, and structural changes before it is expressed in behavior.

A Multilevel Perspective on the Etiology of Schizophrenia

In the remainder of this article, we will attempt to apply the concepts and terminology of multilevel causation outlined above to a number of issues in etiologic research on schizophrenia. The issues highlighted herein were chosen from among the domains of our own research program that may be of heuristic value in the context of a discussion of levels of analysis. Although this overview provides relatively broad coverage of the causal influences thought to play a role in schizophrenia and their possible modes of integration, this overview is not intended to be exhaustive in either respect.

The first question to consider is, what is known about the etiology of schizophrenia that indicates that different causal influences, operating through different mechanisms, are likely to be involved? Genetic epidemiologic studies have demonstrated that schizophrenia is substantially, although not completely, heritable (Cannon, Kaprio, Lonnqvist, Huttunen, & Koskenvuo, 1998; Kendler & Diehl, 1993). The familial recurrence pattern of schizophrenia is not attributable to Mendelian dominant or recessive inheritance of a single major gene (Risch, 1990). Rather, the bulk of epidemiological evidence points to polygenic inheritance, whereby multiple genes of small effect contribute to increasing risk for the disorder but only result in its overt expression if their combined effects cross a hypothetical "threshold of liability." It is possible that different combinations of such genes may be conducive to schizophrenia, a situation referred to as genetic (or locus) heterogeneity. Further, some predisposing genotypes may be transmitted without an expression of the clinical phenotype (Cannon, Zorilla, Shtasel, Gur, Gur, Marco, Moberg, & Price, 1994; Gottesman & Bertelsen, 1989). Such a genotype may be necessary, but, at least in some cases, it is not sufficient for overt schizophrenia; nongenetic influences must then also participate. Some of the most prominent nongenetic influences thought to play a role in schizophrenia occur during gestation and birth and are thus separated from onset of the clinical disorder by some 15–20 years (Cannon, 1997). Putative causal influences more proximal to the expression of clinical symptoms include disturbances at many different levels of the nervous system, such as structural volumetric changes, anomalous receptor distributions, and disturbed functioning in several brain regions (Cannon, 1996; Harrison, 1999). However, some of these changes also have been observed in the nonsymptomatic first-degree relatives of patients with schizophrenia (e.g., Cannon et al., 1994), indicating that the changes can participate in symptom formation only indirectly. Some may be secondary to the disease process or its treatment, and some may be epiphenomena. It thus remains ambiguous which of the neural disturbances in schizophrenia are necessary or sufficient for disease expression, which of these features are under the control of which gene(s), and under what circumstances and in what manner nongenetic influences also play a role.

This complexity necessitates a strategy that is capable of separating neural features associ-

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ated with an inherited susceptibility from those involved in disease expression and that permits the evaluation of a candidate neural system across multiple levels of analysis simultaneously. That is, we require a framework for determining how the putative proximal mechanisms of schizophrenia derive from its distal primary causes and how the different types of distal and proximal influences coalesce in their mechanisms of behavioral effect. In the paragraphs that follow, we attempt to illustrate how a multilevel causal perspective may inform etiologic research on schizophrenia in three major domains: gene localization, the isolation of nongenetic influences, and the elucidation of neural mechanisms.

Gene localization

Attempts at isolating specific genes that confer vulnerability to schizophrenia have thus far been only moderately successful (Moldin, 1997). Of the handful of positive genetic linkage findings, only a few (e.g., on chromosomes 6p, 8p, and 22q) have been replicated in independent samples, and the linked region spans a relatively large chromosomal segment (~5–10 cM) in each case (Karayiorgou & Gogos, 1997). Efforts to locate and characterize specific genes that confer vulnerability to schizophrenia have been hindered by a number of factors, most notably the lack of means to identify nonpenetrant gene carriers and uncertainties concerning the extent of genetic heterogeneity. In principle, these issues might be resolved by including subthreshold diagnoses that are associated with schizophrenia in family studies (e.g., schizotypal personality disorder) in the definition of affection status and by performing linkage analyses in subsets of families sorted into discrete groups based on certain clinical features of index cases. In practice, broad versus narrow designations of phenotypic affection status have been observed to have little effect on linkage statistics, and differences in the overt clinical characteristics of index cases such as the type and severity of symptoms do not appear to be useful in defining subgroups of families that segregate particular (sets of) predisposing genes.

As discussed previously, genetic influences on behavior are not expressed directly but rather must be transduced into behavioral propensities by means of effects on the CNS. Our strategy has therefore focused on elucidating neurobiological and neuropsychological correlates of genetic predisposition that could be used as phenotypic indicators in linkage studies. This approach represents an explicitly causally integrative strategy, as we are evaluating indicators of putative mechanistic processes mediating between distally causative genetic factors and behavioral phenotypic expression. Such "endophenotypic" markers are more proximal to the mechanism of gene action than clinical diagnostic categories and should thus be more sensitive to variation in underlying genetic determinants than clinical diagnosis. In particular, such indicators should index the degree of genetic liability among both affected and nonaffected family members in linkage studies (Cannon, 1996; Gottesman, McGuffin & Farmer, 1987; Holzman, 1992).

Promising endophenotypic indicators for schizophrenia include disturbances in the prefrontal and temporolimbic systems and their interconnections. Impairments in these systems are relatively prominent against a background of generalized cerebral dysfunction (Cannon, van Erp, Huttunen, Lönnqvist, Salonen, Valanne, Poutanen, Standertskjöld–Nordenstam, Gur, & Yan, 1998), and individuals with acquired lesions in these areas show many of the symptoms characteristic of schizophrenia (Luria, 1980; Roberts, Done, Bruton, & Crow, 1990). Further, similar impairments have been observed in a portion of the nonschizophrenic first-degree relatives of schizophrenics, suggesting that such measures may mark the presence of a genetic diathesis to the illness. However, it remains to be determined whether this familial aggregation reflects heritable (rather than shared environmental) influences, and if so, whether there are two or more independently heritable dimensions of dysfunction. To address these issues, we recently applied a comprehensive neuropsychological battery to representative samples of monozygotic (MZ) and dizygotic (DZ) twins discordant for schizophrenia and demographically similar MZ and DZ control twins (Cannon,

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Huttunen, Lönnqvist, Tuulio–Hennrikkson, Pirkola, Glahn, Finkelstein, Hietanen, Kaprio, & Koskenvuo, 2000). We found that performance deficits on tests of spatial working memory, divided attention, intrusions during verbal memory retrieval, and choice reaction time were correlated within discordant MZ twin pairs and were associated with degree of genetic loading in the cotwins of schizophrenics (i.e., MZ > DZ), both independently of each other and of deficits in general cognitive ability. Additionally, patients performed worse than their MZ cotwins on tests of verbal and visuospatial declarative memory but not on the liability-related measures. These findings suggest the partially independent genetic determination of deficits in at least four cognitive domains in schizophrenia patients and their relatives. A question of major importance for future work is whether the different sets of predisposing genes and associated endophenotypic traits, operating via at least partially distinct neural pathways, summate or interact in the determination of overt schizophrenia.

Isolation of nongenetic influences

Are nongenetic etiologic factors capable of causing schizophrenia on their own, or do they contribute to liability only in concert with genetic factors? If the latter is the case, then how do the genetic and nongenetic influences aggregate together? A nongenetic contribution to schizophrenia must exist in light of the fact that roughly one-third of MZ cotwins of schizophrenics are not affected with a schizophrenia spectrum disorder (Cannon et al., 1998). Of the various environmental factors proposed to be involved in schizophrenia, obstetric complications (OCs) have shown the most robust association (see Cannon, 1997, and McNeil, 1988, for reviews). When specific types of OCs have been examined, both direct and indirect measures of fetal hypoxia have emerged as the strongest predictors, occurring in a larger proportion of patients than exposure to infections during gestation and fetal growth retardation (Cannon, 1997). In our recent work with two birth cohort samples, we found that OCs associated with fetal hypoxia, but not nonhypoxic OCs, predict an increased risk for schizophrenia in adulthood (Cannon, Rosso, Hollister, Bearden, Sanchez, & Hadley, 2000; Rosso, Cannon, Huttenen, Huttenen, Lönnqvist, & Gasperoni, 2000). Further, in both cohorts, the effect of hypoxia-associated OCs on risk for schizophrenia remained significant, even after accounting for the occurrence of nonhypoxic prenatal influences.

Fetal hypoxia and other OCs probably do not cause schizophrenia on their own, because the vast majority of people exposed to such complications do not become schizophrenic (Cannon, 1997). Rather, the majority of the evidence points toward a model whereby genetic and environmental factors combine either additively or interactively to influence disease liability. The additive model predicts that both an increase in the number of disease genes (or lack of protective genes) and an increase in the number or severity of OCs are capable of independently increasing the liability to schizophrenia. In the genotype–environment interaction model, one or more predisposing genes must be present in order for OCs to increase disease liability. Consistent with the interaction model, we have found that OCs are associated with an increased risk for schizophrenia in the offspring of affected parents but not in the offspring of normal control parents (Cannon, Mednick, & Parnas, 1990; Parnas, Schulsinger, Teasdale, Schulsinger, Feldman, & Mednick, 1982). However, these high-risk studies do not exclude the possibility that OCs have a direct influence on disease liability that is simply too small to detect when liability is expressed as the presence versus absence of clinical diagnosis. Nevertheless, it should be possible to determine whether genetic factors and OCs contribute independently or interactively to disease causation by comparing quantitative indicators of liability among individuals with and without a genetic background for schizophrenia and with and without a history of OCs (i.e., as in a factorial analysis of variance design; Cannon, Gasperoni, van Erp, & Rosso, 2001).

In a series of studies, we found evidence

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supporting the genotype–environment interaction model in relation to neuroanatomical markers of schizophrenia. For example, in an early study using computed tomography, the contribution of OCs to ventricular volume was found to scale with an increase in genetic risk defined according to whether neither, one, or both parents were affected with schizophrenia spectrum disorders (Cannon, Mednick, & Parnas, 1989; Cannon, Mednick, Parnas, Schulsinger, Praestholm, & Vestergaard, 1993). More recently, we examined the magnetic resonance images of schizophrenia probands, their unaffected full siblings, and demographically matched control subjects without a personal or family history of treated psychiatric morbidity (Cannon, van Erp, et al., 1998; Cannon et al., 1998; Cannon, van Erp, Rosso, Huttunen, Lönnqvist, Pirkola, Salonen, Valanne, Poutanen, & Standertskjöld–Nordenstam, 2002). Both schizophrenic patients and their full siblings exhibited significant reductions in frontal and temporal lobe gray matter volumes and significant increases in frontal and temporal lobe sulcal cerebrospinal fluid (CSF) volumes, compared to controls, independently of the effects of age, gender, and whole brain volume. Ventricular CSF volume increase and white matter volume reduction, however, were found in schizophrenics but not their unaffected siblings. This pattern of results suggests that frontal and temporal lobe gray matter reductions may reflect the influence of genetic (or shared environmental) factors while ventricular enlargement and white matter deficits appear to be specific to the clinical phenotype and may therefore reflect the influences of unique environmental factors (or factors secondary to illness expression). Subsequent analyses examined fetal hypoxia as a possible intervening environmental mechanism underlying some of these abnormalities (Cannon et al., in press). We found that the temporal lobe gray matter and sulcal CSF volumes of patients and siblings exposed to fetal oxygen deprivation were smaller than the temporal lobe gray matter volumes of those who were not. Hypoxia also appeared to be differentially related to increased ventricular CSF in the patients, and there was a similar but nonsignificant pattern in siblings. In contrast, there were no differences in any of the volumetric measurements of low-risk control subjects with and without hypoxia.

If OCs participate causally in schizophrenia, then why are their neurally disruptive effects separated in time from the onset of diagnostic symptoms and signs by some 15–20 years? Although we can only speculate as to the mechanism(s) involved in the timing of schizophrenia onset, a prominent candidate may be the rate of cortical synaptic "pruning." The latter is a developmental elimination of synapses that peaks around late adolescence in the prefrontal and association cortices (Feinberg, 1982; Huttenlocher, 1979; Keshavan, Anderson, & Pettegrew, 1994). Interestingly, this late neurodevelopmental process coincides with the period of peak risk for the onset of schizophrenia. In light of this temporal contiguity, some investigators have proposed that schizophrenia arises due to excessive pruning, such that a reduction of neuronal synapses below a certain threshold produces psychotic symptomatology (Feinberg, 1982; Keshavan et al., 1994; McGlashan & Hoffman, 2000). Within this framework, variations in the rate of synaptic pruning would vary the age of clinical onset of schizophrenia. Interestingly, excessive pruning is consistent with several brain abnormalities documented in schizophrenia, including prominent reductions in neuropil volume (Selemon & Goldman–Rakic, 1999), pyramidal dendritic spines (Garey, Ong, Patel, Kanani, Davis, Mortimer, Barnes, & Hirsch, 1998), and synaptic protein levels (Glantz & Lewis, 1997). Furthermore, because synaptic pruning involves predominantly glutamatergic synapses (Keshevan et al., 1994), exaggerated pruning could result in glutamate receptor hypofunction, which is a possible cause of striatal dopaminergic hyperactivity and psychotic symptoms in schizophrenia (Csernansky & Bardgett, 1998; Grace, 1991; Olney & Farber, 1995).

We have proposed that the neurotoxic effects of hypoxia-associated OCs may reduce the amount of synaptic pruning required in late adolescence to cross the psychosis threshold, leading to an earlier age at onset of schizo-

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phrenia among individuals at risk (Rosso et al., 2000). In support of this hypothesis, the temporal lobe brain regions that are particularly vulnerable to fetal hypoxia (Volpe, 1995) also have been consistently implicated in schizophrenia (Cannon, 1996). Thus, hippocampal neurons are reduced in number or density following fetal hypoxia (Kuchna, 1994; Yue, Mehmet, Penrice, Cooper, Cady, Wyatt, Reynolds, Edwards, Squier, 1997), as they appear to be in the schizophrenic brain (Falkai & Bogerts, 1986; Jeste & Lohr, 1989). These cellular findings are consistent with the in vivo data from our laboratory as summarized above, indicating an association between fetal hypoxia and temporal gray matter deficits in both schizophrenics and their unaffected siblings but not in comparison to subjects at low genetic risk for schizophrenia (Cannon et al., in press). Preschizophrenics with a history of fetal hypoxia may therefore have a lower baseline number of neurons and synapses in the temporal brain regions than those without such a history. With this reduced neuronal reserve, less synaptic pruning due to normal or aberrant developmental processes during adolescence would be required to cross the psychosis vulnerability threshold, resulting in earlier clinical onset in individuals with the schizophrenia genotype. In the terminology of multilevel causation, the effects of the distal nongenetic influences are first transduced into a fixed vulnerability trait (i.e., decreased cortical synaptic density), that is, by itself, not of sufficient severity to provoke symptom formation. Instead, this distal vulnerability trait interacts with normal or aberrant neuronal maturational processes later in life, more proximally to the onset of disease expression, as part of a developmental cascade.

Elucidation of neural mechanisms

Several lines of evidence suggest working memory and the dorsolateral prefrontal cortex (DLPFC) in particular as a potential locus of dysfunction in the pathophysiology of schizophrenia. At the descriptive level, schizophrenic patients appear to have a basic deficit in strategic processing, such as inadequate filtering of irrelevant stimuli or maintenance of a goal directed line of thought. A number of investigators suggested that these strategic deficits reflect a failure to utilize contextual information to guide ongoing behavior (Cohen & Servan–Schreiber, 1992, 1993; Gray, Feldon, Rawlins, Hemsley, 1991). Early attempts to evaluate this context-processing deficit model utilized classical and incidental learning paradigms that could also be applied in rodents. These studies yielded results suggesting that some schizophrenic patients, like animals with experimentally induced lesions producing hyperactivity in the mesolimbic dopamine system, fail to show the inhibition of learning expected to result from preexposure to the test stimulus in a different context (Buhusi, Gray, Schmajuk, 1998). More recently, Cohen and Servan–Schreiber (1992, 1993) operationalized context processing as an aspect of working memory. In this model, an internal representation of context is maintained in working memory and utilized by executive processes in the strategic allocation of attention and other processing resources.

In neuropsychological studies, while schizophrenic patients have been found to show performance deficits on nearly all measures of functioning, against this background of generalized deficit, working memory, attention, abstraction, learning and memory, and language functions appear to be more severely affected (e.g., Saykin, Gur, Gur, Mozley, Mozley, Resnick, Kester, & Stafiniak, 1991; Saykin, Shtasel, Gur, Kester, Mozley, Stafiniak, & Gur, 1994). Working memory dysfunction might in fact underlie performance deficits in other domains such as abstraction, attention, and language, because covarying measures of the former tends to eliminate patient-control differences on the latter (Condray, Steinhauer, van Kammen, & Kasparek, 1996; Gold, Carpenter, Randolph, Goldberg & Weinberger, 1997; Stone, Gabrielli, Stebbins, & Sullivan, 1998).

More direct evidence of involvement of the prefrontal cortex in schizophrenia comes from functional and structural neuroimaging studies. Although the observation of hypoactivity of prefrontal cortex at resting baseline in some patients is not highly reproducible and

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may be secondary to medication and/or chronicity effects (Ingvar & Franzen, 1974; Weinberger & Berman, 1996), there is consistent evidence that schizophrenic patients fail to activate DLPFC to the degree seen in normals when performing the Wisconsin Card Sort Task (WCST; Rubin, Holm, Friberg, Videbech, Andersen, Bendsen, Stromso, Larsen, Lassen, & Hemmingsen, 1991; Weinberger, Berman, & Zec, 1986). In a functional neuroimaging study of MZ twins who were discordant for schizophrenia, the affected twin exhibited less DLPFC activation during the WCST than their cotwin in each of the 10 pairs (Berman, Torrey, Daniel, & Weinberger, 1992). Only one functional neuroimaging study has thus far appeared employing specifically a task of working memory in schizophrenic and control subjects. It showed that, once the movement artifact was eliminated, patients were found to show less activation in DLPFC on functional magnetic resonance imaging during maintenance of verbal material in working memory (Callicott, Ramsey, Tallent, Bertolini, Knable, Coppola, Goldberg, van Geldern, Mattay, Frank, Moonen, & Weinberger, 1998).

At the structural–anatomical level, schizophrenic patients show a variety of volumetric changes throughout the brain, including reduced cortical, hippocampal, and thalamic volumes and increased sulcal and ventricular volumes (Pfefferbaum & Marsh, 1995). Recent neuroimaging work indicates a relatively greater degree of reduction in the frontal and temporal cortical volumes compared with the posterior cortical volumes (e.g., Cannon, van Erp, et al., 1998b). Interestingly, global and dorsolateral prefrontal volumetric deficits have been found to correlate with performance deficits on tests sensitive to working memory processes (i.e., executive, attentional, and context-based recall tests; Maher, Manschreck, Woods, Yurgelun–Todd, & Tsuang, 1995; Seidman, Yurgelun–Todd, Kremen, Woods, Goldstein, Faraone, & Tsuang, 1994). It was recently suggested that a reduction of interneuronal neuropil underlies findings of prefrontal volume reduction in schizophrenia and results in the hypoactive dopaminergic modulation of pyramidal cell activity (Goldman–Rakic & Selemon, 1997). Several neuropathology studies have reported increased prefrontal neuronal density along with decreased thickness of the prefrontal cortex in schizophrenic patients (Benes, McSparren, Bird, SanGiovanni, & Vincent, 1991; Davis & Lewis, 1995; Selemon, Rajkowska, & Goldman–Rakic, 1995, 1998), and a negative finding (Benes, Davidson, & Bird, 1986) has been attributed to methodological weakness (Williams & Rakic, 1988). These alterations are proposed to reflect a neuropil deficit, an interpretation that is consistent with findings of reduced pyramidal spines (Glantz & Lewis, 1997), decreased synaptic protein levels (Garey, Ong, Patel, Kanani, Davis, Hornstein, & Bauer, 1995; Glantz & Lewis, 1995), and increased cell membrane catabolism (Keshavan, Pettegrew, Panchalingam, Kaplan, & Bozik, 1991; Pettegrew, Keshavan, Panchalingam, Stychor, Kaplan, Tretta, & Allen, 1991; Williamson, Pelz, Mersky, Morrison, & Conlon, 1991). Moreover, increases in neuronal density are particularly pronounced in cortical layers where pyramidal neurons receive dopaminergic inputs (Selemon, et al., 1998) and extend glutamatergic projections (Selemon, et al., 1995), suggesting a reduction of pyramidal dendritic and axonal arborization. In light of evidence that dopamine D1-receptors preferentially localize to pyramidal spines and dendrites, a loss of these receptors secondary to neuropil deficit would be expected in schizophrenics (Goldman–Rakic & Selemon, 1997). In fact, a recent PET investigation of D1-receptors in schizophrenia found significantly decreased binding in the prefrontal cortex of neuroleptic-naïve and medication-free patients (Okubo, Suhara, Suzuki, Kobayashi, Inoue, Teresaki, Someya, Sassa, Sudo, Matsushima, Iyo, Tateno, & Toru, 1997). Notably, D1-receptor reduction predicted negative symptomatology and working memory impairment.

Neuroreceptor studies have also provided preliminary evidence of cortical glutamatergic hypofunction and enhanced striatal dopamine release in schizophrenia. Cortical glutamatergic insufficiency is corroborated by three lines of evidence: (a) there is a report of increased gene expression of *N*-methyl-D-aspar-

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tate (NMDA)-receptor subunits in the prefrontal cortex of schizophrenics, a possible compensatory response to glutamatergic hypofunction or receptor loss (Akbarian, Sucher, Tafazolli, Trinh, Hetrick, Potkin, Sandman, Bunney, & Jones, 1996); (b) results from receptor density studies, while variable across brain regions, are consistent in demonstrating an upregulation of glutamate receptor binding in the frontal cortex of schizophrenic brain tissue (Deakin, Slater, Simpson, Gilchrist, Skan, Royston, Reynolds, & Cross, 1989; Nishikawa, Takashima, & Toru, 1983; Simpson, Slater, Roynston, & Deakin, 1991; Toru, Watanabe, Shibuya, Nishikawa, Noda, Mitsushio, Ichikawa, Kurumaji, Takashima, Mataga, & Ogawa, 1988), with one report of unaltered prefrontal non-NMDA glutamate receptor binding (Healy, Haroutunian, Powchik, Davidson, Davis, Watson, & Meador–Woodruff, 1998), and (c) there is evidence of reduced presynaptic glutamatergic function in schizophrenia, including increased frontal glutamate uptake (Deakin et al., 1989), reduced frontal levels of glutamate (Tsai, Passani, Slusher, Carter, Kleinman, & Coyle, 1995), and decreased NMDA-mediated glutamate release from synaptosomes of postmortem samples of prefrontal cortex (Sherman, Davidson, Baruah, Hegwood, & Waziri, 1991). Together with evidence that corticostriatal glutamatergic projections modulate subcortical dopamine release (Carter, 1982; Grace, 1991; Kaliva, Duffy, & Barrow, 1989; Karreman & Moghaddam, 1996; Monaghan & Cotman, 1985; Sesack & Pickel, 1992; Taber & Fibiger, 1993) and that the systemic administration of ketamine and other NMDA-antagonists enhances extracellular dopamine concentration (Verma & Moghaddam, 1996), resulting in focal activation of the prefrontal cortex and perceptual distortions in healthy volunteers (Breier, Molhatra, Inals, Weisenfeld, & Pickar, 1997) as well as symptom exacerbation in schizophrenic patients (Lahti, Holcomb, Medoff, & Tamminga, 1995; Malhotra, Pinals, Adler, Elman, Clifton, Pickar, & Breir, 1997), these findings support the hypothesis that a primary NMDA-receptor insufficiency gives rise to hyperactive subcortical dopamine neurotransmission in the pathophysiology of schizophrenic symptoms (Breier, Adler, Weisenfeld, Su, Elman, Picken, Malhotra, & Pickar, 1998; Carlsson, 1995; Grace, 1991; Olney & Farber, 1995). In schizophrenia patients, significantly higher than normal striatal synaptic dopamine release has been demonstrated in vivo following amphetamine administration (Breier et al., 1997; Laruelle, Abi–Dargham, van Dyck, Gill, D'Souza, Erdos, Krystal, Charney, & Innis, 1996).

The question that naturally arises in this context is whether there is a differential causal role of abnormalities in this brain area at the different levels of analysis (e.g., structural, physiologic, cellular, molecular). Developing an answer to this question rapidly becomes extraordinarily complex. On one hand, there would appear to be a natural hierarchy of effects such that behavior depends on physiology, which in turn depends on structure, in which case it may be reasonable to consider the structural changes as having causal primacy. On the other hand, altered physiology of this region may be a sine qua non for psychotic symptom formation, and this altered physiology may be achievable, with psychotic consequences, by means other than structural neuronal changes (e.g., altering cellular interactions). Although in principle these alternatives could be segregated by conducting statistical tests of mediation, ambiguity is likely to remain due to intrinsic differences in precision of measurement and specificity or proximity to the mechanism of behavioral effect between the measured constructs from the different levels of analysis. Further, in some situations, the relationship between abnormalities across levels of analysis may be inextricably bidirectional, in which case no single level may ever be deemed as having causal primacy (Cicchetti & Cannon, 1999). It is tempting in such situations to conceptualize the abnormalities as "opposite sides of the same coin"; that is, as different perspectives of the same phenomenon.

The above discussion engages the possible causal significance of one particular brain region in schizophrenia, namely, the prefrontal cortex. Of course, we already know that damage to this area, by itself, is not sufficient to

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produce enduring psychotic symptoms. The DLPFC probably contributes causally to schizophrenia, but its causal role is unlikely ever to be understood in isolation. The complex behavioral phenomena of schizophrenia are simply not tractable to a traditional lesion model. Progress in this area depends critically on the development and testing of multisystem models in which we evaluate the modes of causal integration among multiple affected brain systems.

Conclusions

The multifactorial etiology of schizophrenia presents psychopathology researchers with a problem that, thus far, has been difficult to unravel. Identifying individual causative influences entails the disentanglement of a multiplicity of genetic and nongenetic factors interacting in unknown fashion and manifesting effects at levels of analysis spanning the molecular through the behavioral. This challenge is further compounded for schizophrenia, a disorder whose distal causes predate its manifestation by decades and whose proximal predictors may result from the synergism of these initiating factors with subsequent neurodevelopmental and/or psychosocial influences.

Based on the foregoing, we have proposed that a multilevel causal perspective is required for the development and advancement of a fully nuanced theory of schizophrenia etiology and pathophysiology. Within the context of our own research, the application of this integrative strategy has shaped a conceptual framework that incorporates the interaction of distal (i.e., genetic risk, fetal hypoxia) and proximal (e.g., gray matter reduction) predictors of schizophrenia across multiple levels of analysis. In light of our findings to date, the resultant differentiation of vulnerability and disease related indicators holds considerable promise for the specification of genetic factors, nongenetic influences, and neural mechanisms in the etiology and pathophysiology of schizophrenia.

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